

Implementation of Current ENETS Guidelines for Surgery of Small (≤ 2 cm) Pancreatic Neuroendocrine Neoplasms in the German Surgical Community: An Analysis of the Prospective DGAV StuDoQ|Pancreas Registry

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Abstract

Background ENETS guidelines recommend parenchyma-sparing procedures without formal lymphadenectomy, ideally with a minimally invasive laparoscopic approach for sporadic small pNENs (≤ 2 cm). Non-functioning (NF) small pNENs can also be observed. The aim of the study was to evaluate how these recommendations are implemented in the German surgical community.

Methods Data from the prospective StuDoQ|Pancreas registry of the German Society of General and Visceral Surgery were analyzed regarding patient's demographics, tumor characteristics, surgical procedures, histology and perioperative outcomes.

Results Eighty-four (29.2%) of 287 patients had sporadic pNENs ≤ 2 cm. Forty-three (51.2%) patients were male, and the mean age at diagnosis was 58.8 ± 15.6 years. Twenty-five (29.8%) pNENs were located in the pancreatic head. The diagnosis pNEN was preoperatively established in 53 (65%) of 84 patients. Sixty-two (73.8%) patients had formal pancreatic resections, including partial pancreaticoduodenectomy or total pancreatectomy (21.4%). Only 22 (26.2%) patients underwent parenchyma-sparing resections and 23 (27.4%) patients had minimally invasive procedures. A lymphadenectomy was performed in 63 (75.4%) patients, and lymph node metastases were diagnosed in 6 (7.2%) patients. Eighty-two (97.7%) patients had an R0 resection. Sixty (72%) tumors were classified G1, 24 (28%) tumors G2. Twenty-seven (32.2%) of 84 patients had postoperative relevant Clavien–Dindo grade ≥ 3 complications. Thirty- and 90-day mortalities were 2.4% and 3.6%.

Conclusions ENETS guidelines for surgery of small pNENs are yet not well accepted in the German surgical community, since the rate of formal resections with standard lymphadenectomy is high and the minimally invasive approach is underused. The attitude to operate small NF tumors seems to be rather aggressive.

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Introduction

Pancreatic neuroendocrine neoplasms (pNENs) are rare and account for approximately 5% of all pancreatic tumors [1]. According to an analysis of the SEER database, the incidence of neuroendocrine tumors (NETs) is increasing and the age-adjusted annual incidence of pNENs in the USA is 0.32 per 100,000 [1]. An epidemiological survey conducted in Japan showed that the number of patients with newly developed non-functional pNEN in 2010 was approximately 1.7-times higher than in 2005 [2]. An estimated 70 to 80% of pNENs are non-functional and up to 64% of patients present with metastatic disease at diagnosis [1, 3, 4]. Although functional neuroendocrine tumors require resection regardless of size, the management of small (≤ 2 cm) non-functional tumors remains controversial [5]. ENETS guidelines from 2012 [6] and 2016 [7] suggest active imaging-based surveillance as the preferred treatment option for non-functioning asymptomatic G1/low G2 tumors ≤ 2 cm in size. The more recent ENETS consensus guidelines for the standard of care regarding surgery for pNENs suggest that conservative management should be considered for asymptomatic, non-functioning pNENs ≤ 2 cm in patients with MEN1 and for selected patients (significant comorbidity, advanced age) with the sporadic form [8]. ENETS guidelines recommend parenchyma-sparing resections and minimally invasive procedures for suitable small pNENs, especially those in the left pancreas [7, 8]. Formal lymphadenectomy is only recommended in case of proven lymph node metastases. The aim of the present study was to evaluate how these ENETS guidelines for small (≤ 2 cm) pNENs are implemented in the German surgical community.

Materials and methods

The StuDoQIPancreas registry

The StuDoQIPancreas registry of the German Society of General and Visceral Surgery (DGAV) is designed as a prospectively maintained multicenter database with web-based data entry [9]. Data are entered in pseudonymized form at the institutional level without an over-institutional identifier [9]. All institutions had to confirm the correct annual number of entered pancreatic resections by a written confirmation of the hospitals controlling. Sixty-two (20.7%) of about 300 departments of surgery who perform pancreatic surgery in Germany [10] participated in the StuDoQIPancreas registry until June 2017. Of those, 43 institutions enrolled patients with pNENs and provided data that were retrospectively extracted from the

prospective StuDoQIPancreas registry. Sixteen of 36 university departments contributed to the current study. Data of patients with pNENs ≤ 2 cm were analyzed regarding demographics, preoperative imaging, types of surgical procedures, histology, and perioperative outcome.

Definitions

Diagnosis of functional pNENs was based on clinical syndromes, laboratory parameters and/or histopathological features. Due to the assembly of the registry, very rare functioning tumors such as pancreatic gastrinoma, vipoma and glucagonoma were not specifically documented. TNM staging was assessed according to the WHO 2010 classification [11]. The grading system proposed by the International Study Group of Pancreatic Fistula (ISGPF) [12] was used to classify postoperative pancreatic fistulas (POPF) into grades A, B and C. Delayed gastric emptying (DGE) as well as postpancreatectomy hemorrhage (PPH) was defined according to the proposed definitions of the International Study Group of Pancreatic Surgery (ISGPS) [13, 14]. Postoperative complications were defined according to the Clavien–Dindo classification system [15].

Statistical analysis

Continuous variables are presented as means (standard deviation) and categorical variables as proportions. Quantitative variables were compared using the Student's *t* test and qualitative variables (e.g., gender) using the Chi-square test or Fisher's exact test as appropriate. All reported probability values (*p* values) are based on two sided tests, and the level of statistical significance was set at $p < 0.05$. Analyses were performed using SPSS 23.0 (IBM Chicago, 2017).

Results

Patient and tumor characteristics

In a 4-year period (April 2013–June 2017), 287 patients with pancreatic resections for pNENs from 43 institutions in Germany were enrolled in the StuDoQIPancreas registry. The annual case load of participating institutions ranged between 10 and 284 pancreatic resections (Fig. 1). Among 287 patients, 84 (29.2%) with sporadic pNENs ≤ 2 cm were the focus of the current study. Forty-three (51.2%) patients were male, and the mean age at diagnosis was 58.8 ± 15.6 years. Eleven (13.1%) patients had an insulinoma and 73 (86.9%) patients a non-functioning pNEN. Thirty of 73 (41.2%) patients with NF-pNENs were above 65 years. Mean body mass index (BMI) was 27 ± 5.4 kg/

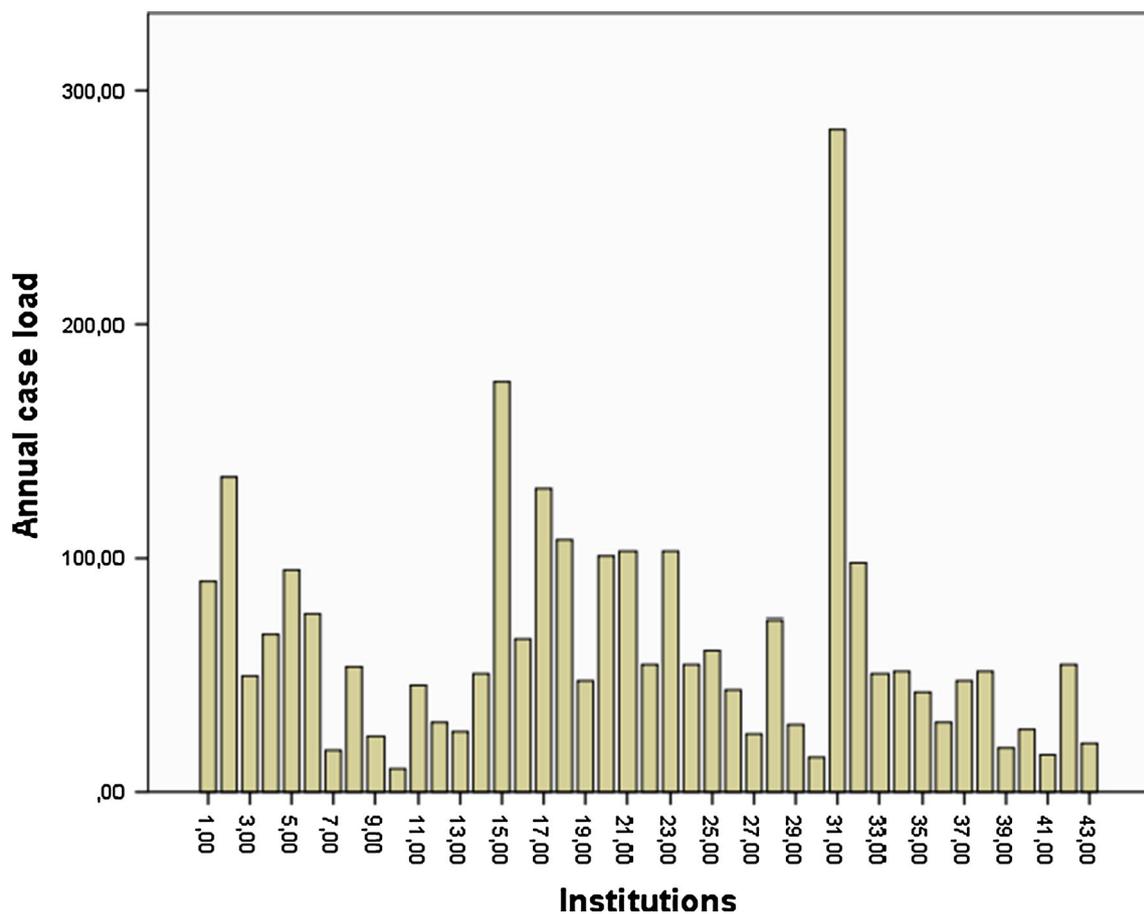


Fig. 1 Annual case load of participating institutions

m². Forty-nine (58.3%) of 84 patients were classified as ASA II, 27 (32.1%) as ASA III, whereas only 8 (9.5%) patients were considered to be ASA I according to the American Society of Anaesthesiologists physical status classification system. Twenty-four (28.6%) patients presented with unclear abdominal discomfort, and the remaining 60 (71.4%) patients were free of abdominal symptoms at time of diagnosis. None of the 84 patients presented with jaundice. Patient characteristics are shown in Table 1.

All tumors were preoperatively localized by imaging, including computed tomography, magnetic resonance tomography, endoscopic ultrasound (EUS) and/or Ga⁶⁸ Dotatoc-PET/CT. Preoperative EUS guided fine needle aspiration was obtained in 26 (31%) of 84 patients and confirmed the diagnosis of pNEN in 17 (65.4%) of these patients. Overall, the diagnosis pNEN was preoperatively suggested in 53 (65%) of 84 patients, whereas the other suggested preoperative diagnoses were potentially malignant solid tumor in 26 (28%) patients and cystic pancreatic lesions in 5 (6%) patients. Twenty-five (29.8%) pNENs

were located in the pancreatic head, 29 (34.5%) in the body and 30 (35.7%) in the tail, respectively (Table 1). Preoperative imaging suggested tumors >2 cm in 11 (20.8%) of 53 patients with a preoperative suspected pNEN, although the actual tumor size was ≤2 cm on pathological analysis. By imaging, in 3 (3.6%) patients lymph node metastases and in 2 (2.4%) patients distant metastases to the liver were suspected.

Surgical procedures, pathology and perioperative outcomes

Sixty-two of 84 (73.8%) patients had formal pancreatic resections, including partial pancreatoduodenectomy ($n = 16$, 19%), distal pancreatectomy ($n = 44$, 52.4%), 96% of those with spleen preservation and total pancreatectomy ($n = 2$, 2.4%) as shown in Table 2. Only 22 (26.2%) patients underwent parenchyma-sparing resections, including enucleations in 13 (15.5%) patients and other parenchyma-sparing resections in the remaining 9 (10.7%) patients. In patients above 65 years, 26 (81.3%) of

Table 1 Baseline characteristics of patients with pNENs ≤ 2 cm

Variable	Mean (SD) or number of patients (n, %)
Age (years)	58.8 \pm 15.6
Sex (male)	43 (51.2%)
ASA	
ASA I	8 (9.5%)
ASA II	49 (58.3%)
ASA III	27 (32.1%)
BMI (kg/m ²)	27 \pm 5.4
Symptoms	
Abdominal pain	24 (28.6%)
Hypoglycemia	11 (13.1%)
Location	
Head	25 (29.8%)
Body	29 (34.5%)
Tail	30 (35.7%)
LN metastases suspected by imaging	3 (3.6%)
Distant metastases suspected by imaging	2 (2.4%)

32 patients had formal pancreatic resections. An open approach was performed in 61 of 84 (72.6%) patients. Only 23 (27.4%) patients had minimally invasive laparoscopic or robotic-assisted procedures, including distal pancreatectomy in 17 (73.9%) patients, enucleation in 5 (21.7%) patients and laparoscopic-assisted Whipple procedure in 1 (4.4%) patient, respectively. Overall, in the StuDoQIPancreas registry the rate of minimally invasive procedures for small pNENs was higher (27.4%) than for all other documented entities (8.9%).

Overall mean operation time was 249.9 \pm 101.5 min. Mean operation time in patients with formal pancreatic resections was 251.7 \pm 99.7 min, which was not different compared to patients with parenchyma-sparing resections with 244.9 \pm 108.7 min ($p = 0.79$). Duration of surgery was not significantly different when comparing the open and minimally invasive procedures approach (250.1 \pm 97.3 vs. 249.1 \pm 116.8 min, $p = 0.97$). Mean length of hospital stay was 18 \pm 11 days and was significantly shorter in patients who underwent a minimally invasive procedure (12 vs. 20 days, $p = 0.004$).

Of patients with adequate documented information, 56 of 58 (96.6%) patients had a soft pancreas and 38 (88.4%) of 43 patients a normal diameter (<3 mm) of the Wirsung duct. Eighty-two (97.7%) of 84 patients had a documented R0 resection. All patients had pT1 tumors on pathological analysis. Fifty-nine (72%) tumors were classified G1, 23 (28%) tumors G2 and none G3, respectively. In 63 (75%) of 84 patients, lymphadenectomy with a mean number of 7.3 \pm 6.9 resected lymph nodes was performed. Lymph

Table 2 Surgical procedures, postoperative outcomes and pathological results of resected patients

Variable	Mean (SD) or number of patients (n, %)
Surgical procedures performed	84 (100%)
Formal pancreatic resections	62 (73.8%)
PPD	16 (19%)
Distal pancreatectomy	44 (52.4%)
Spleen-preserving	42 (50%)
With splenectomy	2 (2.4%)
Total pancreatectomy	2 (2.4%)
Parenchyma-sparing resections	22 (26.2%)
Enucleation	13 (15.5%)
Other resections	9 (10.7%)
Open procedure	61 (72.6%)
Minimally invasive procedure ^a	23 (27.4%)
Operation time (min)	249.9 \pm 101.5
Clavien–Dindo (all)	51/84 (60.8%)
Clavien–Dindo I–II	24 (28.6%)
Clavien–Dindo III	20 (23.8%)
Clavien–Dindo IV	5 (6%)
Clavien–Dindo V	2 (2.4%)
POPF (all)	39/84 (46.4%)
Grade A	14 (16.7%)
Grade B	17 (20.2%)
Grade C	8 (9.5%)
DGE grade B/C	7 (8.3%)
PPH grade B/C	7 (8.4%)
Length of stay (days)	18 \pm 11
WHO 2010 grade	
G1	59 (72%)
G2	23 (28%)
Lymph nodes	
Lymphadenectomy	63 (75%)
Resected lymph nodes	7.3 \pm 6.9
Presence of lymph node metastases	6 (7.2%)
R0 resection	82 (97.7%)

PPPD pylorus-preserving pancreaticoduodenectomy, POPF postoperative pancreatic fistula, DGE delayed gastric emptying, PPH post-pancreatectomy hemorrhage, LOS length of hospital stay

^aIncludes laparoscopic, laparoscopic- and robotic-assisted

node metastases were diagnosed in 6 (7.2%) patients (Table 2). Four of those patients had G1 and two patients G2 tumors. In one of the two patients with preoperatively suspected, distant metastases, surgical exploration confirmed the presence of metastatic lesions in the liver.

Twenty-seven (32.2%) of 84 patients had clinically relevant postoperative Clavien–Dindo grade ≥ 3

Table 3 Univariate analysis of factors associated with postoperative complications (Clavien–Dindo) and postoperative pancreatic fistula (POPF)

Variables	Clavien–Dindo		<i>p</i>	POPF		<i>p</i>
	I–II (<i>n</i> = 24)	≥ III (<i>n</i> = 27)		Grade A (<i>n</i> = 14)	Grade B/C (<i>n</i> = 25)	
Age (years)	55 ± 19	59 ± 14	0.44	55 ± 18.5	56 ± 16.5	0.91
Sex (male)	11	15	0.5	6	14	0.44
BMI (kg/m ²)	27.05 ± 6.9	27.7 ± 3.9	0.69	25.72 ± 5.0	27.18 ± 4.7	0.37
ASA						
ASA I	1	4	0.7	2	2	0.65
ASA II	15	13		9	17	
ASA III	8	10		3	6	
Operation time (min)	260 ± 112.1	263.5 ± 120.4	0.92	273.5 ± 119	270.6 ± 117.2	0.94
Type of surgery						
Formal resections	17	21	0.58	9	18	0.63
Parenchyma-sparing resections	7	6		5	7	
Surgical approach						
Open	15	22	0.14	9	18	0.63
Minimally invasive	9	5		5	7	
LOS (days)	14.7 ± 5.6	25.7 ± 13.8	0.001	19 ± 12.9	21 ± 12.6	0.69

complications that were not statistically different between patients with formal pancreatic resections and patients with parenchyma-preserving resections (33.9% vs. 27.3%, $p = 0.75$, Table 3). Clinically relevant postoperative pancreatic fistulas (grade B/C) were reported in 25 (29.8%) and POPF grade A in 14 (16.7%) of 84 patients (Table 2). DGE grade A was documented in 6 (7.1%) of 84 patients, grade B in 6 (7.1%) and grade C in 1 (1.2%) patient. PPH grade B was documented in 2 (2.4%) and grade C in 5 (6.0%) of 84 patients. Surgical site infections were reported in 9 (10.7%) of 84 patients, all of whom underwent an open approach ($p = 0.08$). Thirty- and 90-day mortalities were 2.4% and 3.6%.

Discussion

ENETS guidelines with its updates for the managements of pNENs exist since 2004 [6, 7, 16] and appear widely accepted. The prospective StuDoQIPancreas registry provides the unique opportunity to give a quite representative picture of the current clinical practice of pancreatic surgery in medium and high volume centers throughout Germany. In the present study, based on the data of 43 surgical departments, we analyzed for the first time, whether the ENETS recommendations for the treatment of small (≤ 2 cm) pNENs are implemented in the German surgical community.

First, the ENETS guidelines [6, 7] as well as the ENETS consensus guidelines for standard of care for surgery for

small pNEN stated that active surveillance as a treatment option should be considered for sporadic asymptomatic, non-functioning pNETs ≤ 2 cm with low grade differentiation (G1, low G2) for selected patients, especially for patients with significant comorbidity and/or advanced age [8]. This recommendation is based on several studies [17, 18] and one systematic review [19] showing no increased potential of malignant transformation in these tumors during a follow-up of up to 5 years. In the present study, the proportion of resected small pNENs among all resected pNENs was quite high (29.2%, 84 of 287) and 73 (86.9%) patients had asymptomatic, non-functional pNENs ≤ 2 cm. Of those, 30 (41.2%) patients were above 65 years and 20 (69%) of those had G1 tumors. At least these latter patients would have been good candidates for an active surveillance. Although the registry does not provide data on the number of patients who optioned for surveillance, one can assume based on these data that observation is yet not a well-accepted option for German surgeons. What might be the reasons for this attitude? The main reason might be that several retrospective series have shown a significant risk of malignant transformation in small pNENs [20, 21] with lymph node metastases up to 24% in well differentiated tumors less than 2 cm [22]. In the present study, 6 (7.2%) patients had lymph node metastases upon pathological examination. Thus, one can speculate that many surgeons still believe that these small pNENs should better be resected. However, the prognostic relevance of these micrometastases is still unclear and a matter

of debate [7]. Another reason why surgery was indicated in the present study is the fact that the preoperative diagnosis of pNEN has only been established in 65% of patients. One might speculate that in several cases not all available preoperative diagnostic modalities were used to determine the nature of the lesion and its malignant potential. For example only 26 (31%) of 84 patients underwent EUS guided-FNA, which would have allowed for a more precise preoperative tumor classification [23, 24]. It is also of note that preoperative CT imaging overestimated the tumor size in 11 (20.8%) of 53 patients with the preoperative diagnosis of pNEN, suggesting tumor size >2 cm, so that surgery was indicated in line with current ENETS recommendations [6, 7]. The problem of tumor size overestimation by preoperative imaging has been already reported for pNENs associated with the MEN1-syndrome [25]. The above-mentioned facts demand the discussion of the indication for an operation of a small pancreatic lesion in an interdisciplinary board which considers the patients constitution, the malignant potential of the tumor and the risk of postoperative complications. The latter is still significant, since 32% of patients experienced relevant postoperative complication and the 90-day mortality was 3.6%.

Second, current ENETS guidelines for surgery of small pNENs recommend parenchyma-sparing resections when technically feasible to avoid endocrine and exocrine pancreatic insufficiency [7]. In the present study, however, the rate of parenchyma-sparing resections was only 22.2% and as low as 18.7% in patients above 65 years. These rates are much lower than the recently reported 42.3% rate of parenchyma-sparing procedures in a multicenter retrospective analysis from 16 European tertiary referral centers [26], suggesting that several patients were overtreated. One reason for the wide use of formal pancreatic resections among German surgeons might be the conviction that formal pancreatic resections are associated with less complications than parenchyma-sparing resections, especially enucleations. In the present study, however, parenchyma-sparing resections and formal resections had similar postoperative clinically relevant Clavien–Dindo grade ≥ 3 complication rates (27.3% vs. 33.9%, $p = 0.75$), which is in line with a recent systematic review and meta-analysis that demonstrated similar complication and mortality rates comparing enucleations and formal resections for small pancreatic lesions [27]. The presented 32.2% rate of relevant postoperative Clavien–Dindo ≥ 3 complications is higher than the 14.3% rate reported in a recent multicenter study [26], but still lower than the 50% rate suggested by the ENETS standard of care guideline [8]. Given the recently reported mortality rate of 10.1% after pancreatic resections in Germany between 2009 and 2013 [28], the 90-day mortality rate of 3.6% in the present study has to be considered acceptably low. This is especially true, if one

considers that 43 surgical departments enrolled patients and that surgery for pNENs is considered to be high risk because of a generally soft pancreas and a normal diameter of the Wirsung duct.

Third, ENETS standard of care guidelines [8] recommend nodal sampling and frozen section during parenchyma-sparing pancreatic resections in the presence of suspicious lymph nodes, and a standard lymphadenectomy is only recommended in case of proven lymph node metastases. In the present study, however, a lymphadenectomy was performed in 75% of patients and 7.2% of those showed lymph node metastases on pathological examination. Similarly, in a recent European multicenter study including 210 with resected small non-functioning pNENs 65% of patients underwent lymphadenectomy with a mean of 6 harvested lymph nodes and lymph node metastases in 10.6% of patients [26].

Fourth, ENETS standard of care guidelines recommend a minimally invasive procedure for preoperatively localized small pNENs, especially if located in the pancreatic body and tail [6, 7]. This was also recommended by a former consensus conference of German pancreatic surgeons [29]. Therefore, it was somehow discouraging that in the present study, a minimally invasive approach was only applied in 23 (27.4%) patients, although 70% of those tumors were located in the left pancreas. A recent systematic review and meta-analysis showed that the laparoscopic approach is associated with lower overall complication rates, lower blood loss and shorter length of hospital stay [30]. In the present study, minimally invasive procedures were only associated with a shorter length of hospital stay. The complication rates, however, were not significantly different, possibly due to the limited number of laparoscopic resections performed and the relative small sample size. There is certainly room for improvement in the German surgical community with regard to the use of the minimally invasive approach for small pNENs.

The present study has certain limitations. The retrospective analysis and the relatively small sample size exclude definitive conclusions. Moreover, the StuDoQIPancreas registry provides only data of resected patients, which precludes any comparison between resected and patients under surveillance during the same time period in the participating centers. Thus, one can only speculate regarding the number of patients under surveillance. The incidence of pNENs in Germany is currently approximately 0.02 per 100,000 inhabitants per year [31]. In the German NET Registry were 687 pNENs from 35 NET centers between 1999 and 2010 enrolled, of which 60% were non-functioning tumors [32]. According to our study and the SEER database [33], the rate of pNEN <2 cm ranges between 20 and 30%. Based on these numbers, one can calculate that about 300 non-functioning small pNENs

will be diagnosed in Germany per year. Since the StuDoQIPancreas registry covers only 15% of pancreatic resections performed in Germany [9], one might speculate the about 600 small pNENs had been resected in the reported time period in Germany and another 600 (50%) underwent surveillance. This speculated surveillance rate would be in the range of a previous systematic review comparing active surveillance and surgery for small pNENs based on 5 retrospective studies that reported surveillance rates of 25–58% [19].

In conclusion, ENETS guidelines for surgery of small pNENs are yet not well accepted in the German surgical community, since the rate of formal resections with standard lymphadenectomy is high and the minimally invasive approach is underused. The attitude to operate small NF-pNENs, especially in the elderly, seems to be quite aggressive.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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